

# Bilirubin levels in patients with mild and severe Covid-19: A pooled analysis

Dear editor

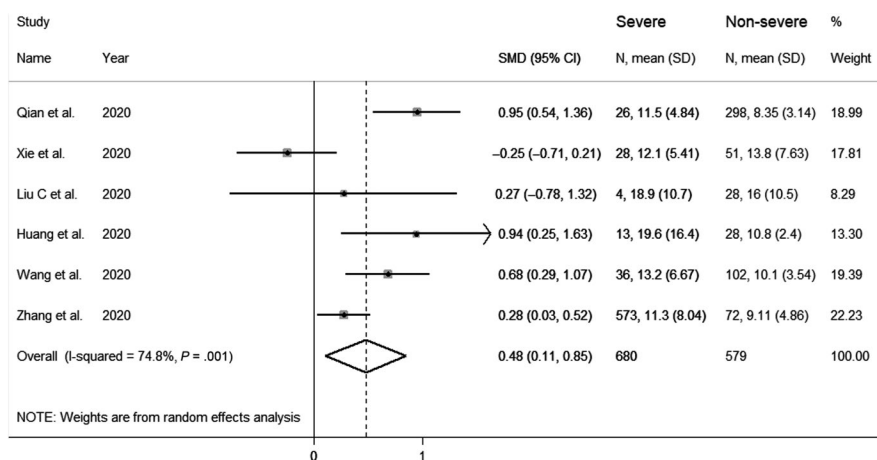
We read with interest the commentary by Sun et al regarding the impact of coronavirus disease 19 (Covid-19) on liver function<sup>1</sup>; the authors gave a brief insight of the alterations in several liver function biomarkers described in the current literature. Bilirubin levels have been found altered in patients with Covid-19,<sup>1</sup> but the dynamics of such alteration are not clear, especially in relation to the severity of the disease. To understand this, we performed a pooled analysis of studies retrieved in Medline (Pubmed), Scopus and Web of Science databases from January 1, 2020 to April 11 2020, reporting bilirubin levels in patients with and without severe Covid-19. The keywords used were 'bilirubin' and 'coronavirus' or 'bilirubin' and 'Covid-19'. In all, 19 articles were initially detected, but 12 were excluded as duplicates and three because of lacking data; two further articles were retrieved from reviewing the reference lists, and therefore, six articles were enrolled for analysis.<sup>2-7</sup>

Standardized mean differences (SMD) were used to build forest plots of continuous data and to evaluate differences in bilirubin levels.  $P < .05$  was considered statistically significant, and 95% confidence intervals (CIs) were reported. In five studies,<sup>2,3,5-7</sup> the mean and standard deviation values were extrapolated from median and interquartile range (IQR). Heterogeneity of SMD was tested with Q statistic (significance level at  $P < .10$ ), and the  $I^2$  was calculated. In

analyses with high heterogeneity, a random-effects model was applied. Sensitivity was tested by sequentially excluding one study in each turn. Statistical analyses were performed using Stata 14 (STATA Corp.).

The mean difference in serum bilirubin between Covid-19 patients with or without severe disease is shown in Figure 1. In five studies, patients with severe Covid-19 displayed higher bilirubin levels compared to those with milder forms (mean difference ranging between 0.27 and 0.95  $\mu\text{mol/L}$ )<sup>2,4-7</sup> while in the remaining study the bilirubin concentration was found to be higher in patients with non-severe Covid-19 (mean difference  $-0.25 \mu\text{mol/L}$ ).<sup>3</sup> The pooled results revealed that bilirubin concentration was significantly higher in patients with severe Covid-19 (SMD: 0.48  $\mu\text{mol/L}$ ; 95% CI, 0.11 to 0.85  $\mu\text{mol/L}$ ,  $P = .012$ ). The heterogeneity was high ( $I^2 = 74.8\%$ ;  $P = .001$ ). Sensitivity analysis showed that the effect size was not modified when every single study was in turn removed (effect size ranged between 0.36  $\mu\text{mol/L}$  and 0.62  $\mu\text{mol/L}$ ). Bilirubin concentration remained significantly higher (SMD: 0.53  $\mu\text{mol/L}$ ; 95% CI, 0.04 to 1.03  $\mu\text{mol/L}$ ,  $P = .034$ ;  $I^2 = 76.7\%$ ;  $P = .002$ ) in patients with severe COVID-19 also after excluding the large study of Zhang et al,<sup>4</sup> which accounted for nearly 51% of the overall sample size. The results of this pooled analysis show that bilirubin levels are significantly increased in patients with severe Covid-19.

**FIGURE 1** Forest plot of SMD differences of serum albumin between COVID-19 patients with or without severe disease



**Abbreviations:** CIs, confidence intervals; Covid-19, coronavirus disease 19; IQR, interquartile range; SMD, standardized mean difference.

**KEYWORDS**



liver, bilirubin, coronavirus, Covid-19, Infection

**CONFLICTS OF INTEREST**

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